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An ultrasonic wave-assisted synthesis of *meso*-amidinophenyl substituted porphyrins

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Abstract

With the aid of an ultrasonic irradiation, *meso*-amidinophenyl substituted porphyrins were prepared by the reaction of lithium amide and *meso*-cyanophenyl porphyrins. This approach can give the derivatized porphyrins in very high yields and very short reaction times as compared to the conventional thermal method.

Keywords: Amidino; Porphyrins; Synthesis; Ultrasound

1. Introduction

Porphyrin serves as a functional chromophore in a wide variety of biological systems, the most common being the chlorophyll and heme proteins.[1] They are also important in understanding crucial biological processes and have numerous potential for applications in the catalysis of organic reactions, magnetic resonance imaging and photodynamic therapy.[2] Porphyrin macrocycles are very flexible and by introducing substituents selectively at the β- or *meso*-positions, the properties can be tuned at will for each specific application. Recently, *meso*-amidinophenyl substituted porphyrins were found to be highly valuable for this purpose and have been used in a wide variety of model systems.[3] Moreover, owing to their similar structural motif to 4,6-diamidino-2-phenylindole (referred to as DAPI, an important DNA agent with numerous uses as antibiotic, antiviral, and anticancer drug),[4,5] *meso*-amidinophenyl substituted porphyrins had received much attention on DNA binding and photodynamic therapy.[6] Generally, amidino substituted porphyrins were synthesized in about 60% yield via the treatment of Zn(II)[7a] or Ni(II)[7b] cyano substituted porphyrinate with Weinreb's amide transfer reagent [$AlCl(CH_3)(NH_2)$] (freshly prepared from equimolar amounts of ammonium chloride and $Al(CH_3)_3$ in toluene at 80 °C, for 3–4 days, followed by the addition of concentrated HCl and trifluoroacetic acid (TFA). However, such reactions can be slow and required vigorous reaction conditions and often lead to mixtures of products with poor regioselection. Considering that lithium amidinates can be readily generated in situ through the reaction of lithium amide with α-hydrogen free nitriles RCN,[8] another way of obtaining *meso*-amidinophenyl substituted porphyrins was also developed via the interaction of a slurry of *meso*-cyanophenyl substituted porphyrin with lithium bis-(trimethylsilyl)amide.[9] Unfortunately, due to the effect from the highly conjugated porphyrin ring, the reaction is extremely time-consuming (51 days) and work-up procedures are also complicated, accompanied with a low synthetic yield (28%). Obviously, the method is not available for the preparation of *meso*-tetrakis(amidinophenyl)porphyrin, which cannot be purified on silica gel because of its poor solubility and its strong adherence to silica gel. Ultrasonication is an important technique in organic

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synthesis and has a profound impact on the way chemists approach organic and parallel synthesis. Relative to the traditional thermal heating, reduction in reaction times, improved yields, and suppression of side product are obviously the benefits of this technology.[10] We herein report the use of ultrasonic irradiation in the synthesis of new *meso*-amidinophenyl substituted porphyrins (**1a–6a**) via interaction of lithium amide and *meso*-cyanophenylporphyrins. It should be pointed out that the reaction time was reduced significantly as compared to the conventional thermal method (51 days), and this reaction smoothly proceeded in good to excellent yields at room temperature.

2. Result and discussion

The starting materials such as highly symmetric porphyrin free base 5-(*m*, *o* or *p*-cyanophenyl)-10,15,20-tris(4-tolyl)porphyrin (**1**, **2** or **3**) and 5,10,15,20-tetra(*m* or *p*-cyanophenyl)porphyrin (**5** or **6**) were prepared by direct condensation of the respective benzaldehyde and pyrrole in propionic acid according to the Alder–Longo modified Rothemund procedure and purified by column chromatography using silica gel.[11] The yields are about 6.6–20%. The less symmetric porphyrin free base 5,15-bis(4-cyanophenyl)-10,20-bis(4-tolyl)porphyrin (**4**) was prepared by condensation of the corresponding dipyrromethane and benzaldehyde in dichloromethane in the presence of acid catalysts such as trifluoroacetic acid (TFA) or BF_3 etherate ($BF_3{\cdot}Et_2O$) in an isolated yield of about 44%. ^{1}H NMR analysis showed that **4** was isomerically pure. The precursor 5-tolyldipyrromethane was prepared by TFA acid-catalyzed condensation of benzaldehyde and excess pyrrole according to the procedure of Lee and Lindsey.[12]

The reagent lithium bis(trimethylsilyl)amide [$LiN(SiMe_3)_2$] was freshly prepared in situ from the reaction of bis(trimethylsilyl)amine with an equivalent amount of *n*-BuLi in dry THF, and should be used within 1 h of its preparation. When the subsequent nucleophilic addition reaction was carried out under ultrasonic wave irradiation, in a Branson 1210 Ultrasonic Cleaner (80 W, 47 kHz) at room temperature, the reaction time was reduced remarkably as compared to the conventional thermal method (51 days) and the products were easily isolated by simple washing and filtration. As the starting point of our exploration, we chose the reaction between 5-(4-cyanophenyl)-10,15,20-tris(4-tolyl)porphyrin free base (**1**) and lithium bis(trimethylsilyl)amide (in THF solution) in a 50 mL sealed Schlenk flask, which was placed into an ultrasonic bath at room temperature. The progress of the reaction was monitored by thin layer chromatography (TLC). After sonication for about half an hour, the starting material (**1**) was almost completely transformed into the title product. Meanwhile, the temperature of the ultrasonic bath increased to 45 °C automatically without heating after half an hour of the reaction time. After removal of the solvent, the residue was washed with water and methanol followed by diethyl ether to obtain a purple solid. The compound can be further purified by column chromatography on silica gel, eluting with CH_2Cl_2/methanol, to afford the pure product 5-(4-amidinophenyl)-10,15,20-tris(4-tolyl)porphyrin (**1a**) in >95% yield (Scheme 1). The solubility of **1a** is good in organic solvents such as $CHCl_3$, CH_2Cl_2, DMSO, and methanol. The formation of the amidino functional group was confirmed by NMR spectroscopy. Compound **1a** in DMSO-d_6 showed a singlet at δ 166.5 ppm for the carbon of the amidino group in its ^{13}C NMR spectrum, and two broad singlets of equal intensity (2H each) at δ 9.66 and 9.25 ppm for the N–H protons of the amidino group in its ^{1}H NMR spectrum. The ^{1}H NMR data for the amidino protons further indicated that the amidino group formed strong H-bonds with H_2O molecules present in DMSO (Chart 1).[13]

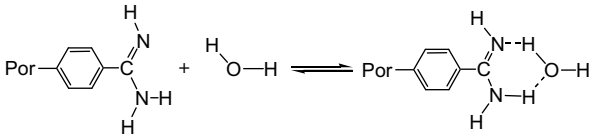
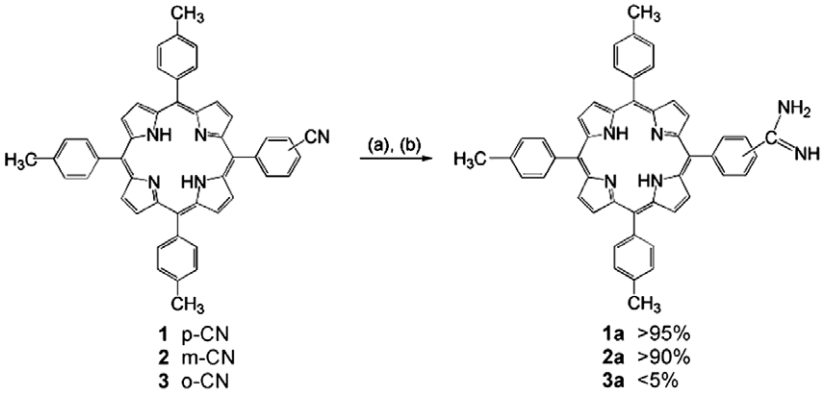


Chart 1.



Scheme 1. Synthesis of *meso*-amidinophenyl monosubstituted porphyrins. Reagents and conditions: (a) 2 equiv of $LiN(SiMe_3)_2$, THF, ultrasonic irradiation for 0.5 h; (b) under air, H_2O.

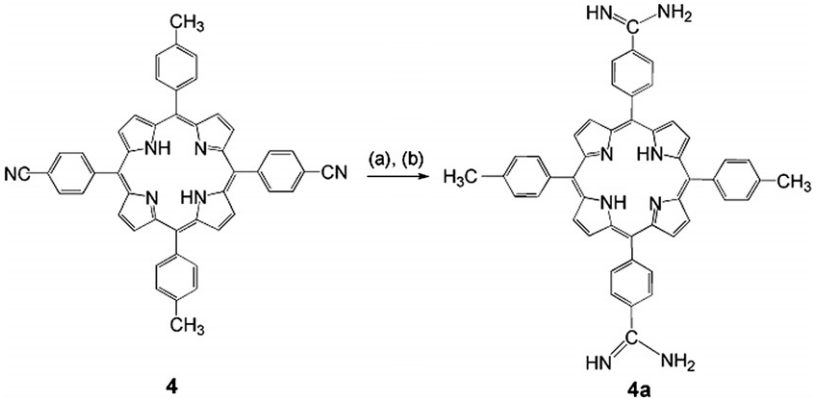
Similarly, when 5-(3-cyanophenyl)-10,15,20-tris(4-tolyl)-porphyrin (**2**) was reacted with lithium bis(trimethylsilyl)amide under irradiation by ultrasonic wave, the corresponding 5-(3-amidinophenyl)-10,15,20-tris(4-tolyl)-porphyrin (**2a**) was also obtained with 90% yield (Scheme 1).[13] However, nothing happened to 2-cyanophenyl mono-substituted porphyrin (**3**) when the same reaction was carried out due to the steric effect.

The reaction between 5,15-bis(4-cyanophenyl)-10,20-bis(4-tolyl)porphyrin (**4**) and lithium bis(trimethylsilyl)-amide gave good results with respect to the yield and the reaction time. After the solvent was removed and the residue washed with acetonitrile and distilled water, 5,15-bis-(4-amidinophenyl)-10,20-bis(4-tolyl)porphyrin (**4a**) was isolated in an almost quantitative yield (Scheme 2). The solubility of **4a** was fairly good in mixed solvents of methanol and dichloromethane, so we could also purify it by column chromatography on silica gel eluting with CH_2Cl_2/methanol (5:1, v/v).[13]

Further insight into the reaction between 5,10,15,20-tetrakis(4-cyanophenyl)porphyrin (**5**) and lithium bis(trimethylsilyl)amide was also obtained. Although the solubility of **5** is low in THF and other organic solvents, the reaction proceeded completely when the reaction solution became clear after the addition of lithium bis(trimethylsilyl)amide in THF. The ESI-HRMS results indicated that neither the starting material nor other side products were detected. After removing the solvent and washing the residue with acetonitrile and distilled water for several times, the title product 5,10,15,20-tetrakis(4-amidinophenyl)porphyrin (**5a**) was obtained almost quantitatively (Scheme 3).[14] However, the solubility of 5,10,15,20-tetrakis(4-amidinophenyl)porphyrin (**5a**) is poor in organic solvents. When protonated with HCl, **5a** achieved a very good solubility in water, which is beneficial for a wide range of biological applications. Similar to **5a**, the compound 5,10,15,20-tetrakis(3-amidinophenyl)porphyrin (**6a**) was also prepared in a high yield within 2 h.[14] A summary of the reaction time and product yield for different substrates is listed in Table 1.

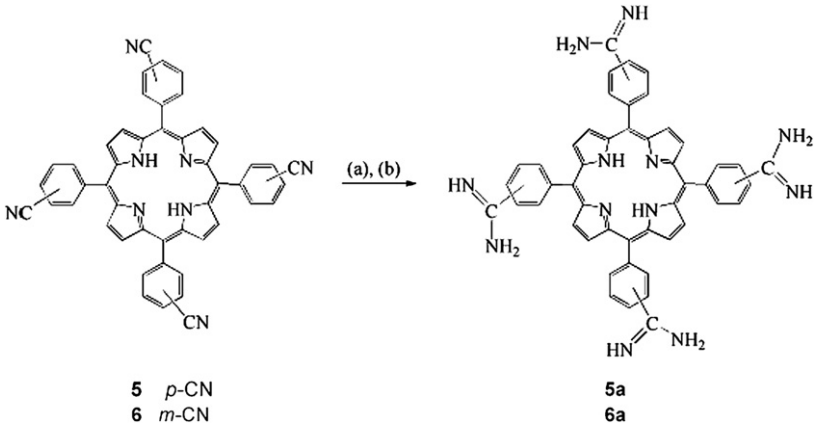
3. Conclusions

In conclusion, an ultrasonic wave-assisted, two-component reaction for the generation of *meso*-amidinophenyl substituted porphyrins has been developed, and found to



4 **4a**

Scheme 2. Synthesis of *meso-trans*-bis(amidinopheny)porphyrin. Reagents and conditions: (a) 2 equiv of $LiN(SiMe_3)_2$, THF, ultrasonic irradiation for 2 h; (b) under air, H_2O.



5 *p*-CN **5a**
6 *m*-CN **6a**

Scheme 3. Synthesis of *meso*-tetrakis(amidinophenyl)porphyrins. Reagents and conditions: (a) 4 equiv of $LiN(SiMe_3)_2$, THF, ultrasonic irradiation for 2 h; (b) under air, H_2O.

Table 1
Ultrasonic wave-assisted synthesis of amidinophenyl substituted porphyrins

Entry	Substrate	Product	Reaction time (h)	Yield (%)
1	**1**	**1a**	0.5	98
2	**2**	**2a**	0.5	90
3[a]	**3**	**3a**	4	2
4	**4**	**4a**	2	95
5	**5**	**5a**	2	93
6	**6**	**6a**	2	92

[a] In entry 3, reaction time was increased to 4 h, but the yield did not increase much.

be both fast and efficient. The method provides tetrakis(amidinophenyl)-derived porphyrins in a pure form. Ultrasonic wave irradiation dramatically reduces the reaction time from 51 days to several hours.

Acknowledgements

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13. *Typical procedure and spectral data for* **1a, 2a** *and* **4a**: A slurry of **1** (or **2**, **4**) (150 mg, 0.22 mmol) and lithium bis(trimethylsilyl)amide (2.0 mL of 0.16 M in THF solution, 0.32 mmol) in dry THF (20 mL) was placed under ultrasonic wave irradiation at room temperature. When TLC indicated that the reaction was completed, the solvent was removed under vacuum. Then the residue was dissolved in $CHCl_3$ and purified by column chromatography on silica gel. The first fraction was collected as a trace amount of the starting material by eluting with chloroform. The next fraction eluted with CH_2Cl_2/methanol (10:1–5:1, v/v) was the desired compound. Compound **1a**: mp >300 °C. HRMS (ESI, +ve mode in CH_3OH) *m/z*: 699.3231 $(M+H)^+$ ($C_{48}H_{39}N_6$ requires 699.3236). ^1H NMR (400 MHz, DMSO-d_6): δ 2.90 (s, 2H, pyrrole ring NH), 2.70 (s, 9H, CH_3), 7.60 (d, $J = 8.1$ Hz, 6H, C_6H_4), 8.05 (d, $J = 8.1$ Hz, 6H, C_6H_4), 8.26 (d, $J = 8.1$ Hz, 2H, C_6H_4), 8.44 (d, $J = 8.1$ Hz, 2H, C_6H_4), 8.75–8.86 (m, 8H, pyrrole ring), 9.25 (br, 1H), 9.66 (br, 1H). ^{13}C–{^1H} NMR (100 MHz, DMSO-d_6): δ 21.7, 118.4, 120.9, 121.3, 127.5, 128.3, 134.8, 138.1, 138.9, 146.5 and 166.5 ppm. IR (KBr): 3317, 3022, 2918, 1673, 1608, 1558, 1473, 1384, 1221, 1182, 966, 800, 733 cm^{-1}. UV–vis in toluene, 20 °C, λ_{max}/nm [log(ε/$dm^3\,mol^{-1}\,cm^{-1}$) in parentheses]: 419 (5.54), 517 (4.12), 551 (3.86), 593 (3.60), 646 (3.64); Compound **2a**: mp >300 °C. HRMS (MALDI-TOF) *m/z*: 657.2783 $(M+H)^+$. ($C_{45}H_{33}N_6$ requires 657.2766). ^1H NMR (400 MHz, DMSO-d_6): δ −2.97 (s, 2H, pyrrole ring NH), 2.70 (s, 9H, CH_3), 7.79–7.85 (m, 9H, C_6H_4), 8.05 (t, $J = 8.0$ Hz, 6H, C_6H_4), 8.19 (m, 6H, C_6H_4), 8.29 (d, $J = 8.0$ Hz, 1H, C_6H_4), 8.56 (d, $J = 7.6$ Hz, 1H, C_6H_4), 8.65 (s, 1H, C_6H_4), 8.82 (s, 8H, pyrrole ring), 9.47 (br, 3H). IR (KBr): 3317, 3022, 1673, 1608, 1558, 1473, 1384, 1221, 1182, 966, 800, 733 cm^{-1}. UV–vis in toluene, 20 °C, λ_{max}/nm [log(ε/$dm^3\,mol^{-1}\,cm^{-1}$) in parentheses]: 419 (5.54), 517 (4.12), 551 (3.86), 593 (3.60), 646 (3.64); Compound **4a**: mp >300 °C. HRMS (MALDI-TOF) *m/z*: 727.3303 $(M+H)^+$ ($C_{48}H_{39}N_8$ requires 727.3297). ^1H NMR (400 MHz, DMSO-d_6): δ −2.82 (s, 2H, pyrrole ring NH), 2.70 (s, 6H, CH_3), 7.55 (d, $J = 7.6$ Hz, 4H, C_6H_4), 8.00 (s, 4H, C_6H_4), 8.08 (d, $J = 8.0$ Hz, 4H, C_6H_4), 8.26 (d, $J = 7.6$ Hz, 4H, C_6H_4), 8.78 (d, $J = 4$ Hz, 4H, C_6H_4), 8.88 (d, $J = 4.8$ Hz, 4H, C_6H_4). ^{13}C–{^1H} NMR (100 MHz, DMSO-d_6): δ 21.6, 119.1, 121.9, 126.1, 128.1, 134.4, 138.1, 139.2, 144.2 and 164.8 ppm. IR (KBr): 3317, 2962, 1668, 1608, 1558, 1472, 1261, 1095, 1021, 966, 800, 730 cm^{-1}. UV–vis in toluene, 20 °C, λ_{max}/nm [log(ε/$dm^3\,mol^{-1}\,cm^{-1}$) in parentheses]: 419 (5.58), 515 (4.23), 550 (3.96), 590 (3.71), 647 (3.69).
14. *Typical procedure and spectral data for* **5a** *and* **6a**: A slurry of **5** (or **6**) (0.21 mmol) and lithium bis(trimethylsilyl)amide (8.0 mL of 0.16 M in THF solution, 1.28 mmol) in dry THF (20 mL) was irradiated with ultrasonic wave at room temperature for 2 h. The solvent was removed in vacuo. The residue was then washed with acetonitrile, distilled water and diethyl ether, purified by crystallization from methanol and acetonitrile. The resulting compound was pure enough for NMR analysis. Compound **5a**: mp >300 °C. HRMS (MALDI-TOF) *m/z*: 783.3456 $(M+H)^+$ ($C_{48}H_{39}N_{12}$ requires 783.3420). ^1H NMR (400 MHz, DMSO-d_6): δ −2.95 (s, 2H, pyrrole ring NH), 8.24

(s, 8H, C_6H_4), 8.26 (s, 8H, C_6H_4), 8.87 (s, 8H, pyrrole ring). ^{13}C–{^1H} NMR (100 MHz, DMSO-d_6): δ 120.4, 126.8, 127.9, 134.8, 145.1 and 168.9 ppm. IR (KBr): 3318, 3201, 1667, 1607, 1507, 1440, 966, 863, 799, 502 cm^{-1}. UV–vis in toluene, 20 °C, λ_{max}/nm [log(ε/dm^3 mol^{-1} cm^{-1}) in parentheses]: 419 (5.40), 515 (4.10), 551 (3.81), 590 (3.63), 645 (3.52); Compound **6a**: mp >300 °C. HRMS (MALDI-TOF) *m*/*z*: 783.3407 $(M+H)^+$ ($C_{48}H_{39}N_{12}$ requires 783.3420). ^1H NMR (400 MHz, DMSO-d_6): δ −2.98 (s, 2H, pyrrole ring NH), 8.81–7.57 (m, 24H, pyrrole ring and phenyl ring). IR (KBr): 3313, 3201, 1668, 1495, 1444, 1087, 868, 801, 491 cm^{-1}. UV–vis in toluene, 20 °C, λ_{max}/nm [log(ε/dm^3 mol^{-1} cm^{-1}) in parentheses]: 419 (5.40), 515 (4.10), 551 (3.81), 590 (3.63), 645 (3.52).